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ORIGINAL ARTICLES

SOME PROBLEMS IN THE PATHOLOGY OF SYPHILIS.[1]

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It is proposed in the present paper to discuss some of the phases of syphilis which have resulted from the intensive investigations of the past ten years. These problems include the question of immunity, a few of the most striking anatomicopathological changes met with in the disease, as well as its effects on the cardiovascular and nervous systems, and the lessons to be deduced from the knowledge which has been gained.

Immunity. One of the most interesting and perhaps least understood problems in the pathology and biology of lues is the question of immunity. Formerly it was taught that like many of the other infections one attack of syphilis conferred a lifelong immunity, that a syphilitic mother might transmit an immunity to her child, while, conversely, the mother of a syphilitic child was rendered insusceptible to the disease, as postulated in the well-known laws of Profeta and Colles-Baumès. Since the work of Neisser, Finger and Landsteiner, Levaditi, Uhlenhuth and Mulzer, and others, however, our conception of immunity in syphilis has undergone considerable modification.

Investigations along these lines and in microbiology have shown that syphilis is closely allied with the protozoal affections, especially those caused by trypanosomes and piroplasomes. These diseases differ from those of bacterial origin in the manner in which they respond to the introduction of organisms into the system. While in the great majority of infectious processes acquired immunity is expressed by a protection more or less absolute against a new attack and the disappearance of the causal agent from the body, or its innocuousness to the host if it persists, diseases of protozoal origin behave in a different way. Levaditi has demonstrated, for instance, that animals suffering with a spirillary infection are immune to a new inoculation. Their serum has a high antibody content, but the blood still harbors parasites and is capable of producing a fresh infection in healthy animals. So with the serum of guinea-pigs inoculated with Nagana or Surra trypanosomes. This is trypanocidal for these organisms *in vitro*, but *in vivo* they have acquired an insensibility to the trypanolytic antibodies, for the blood and tissues of the animals still contain parasites. The same is true of human subjects suffering from sleeping sickness in whose serum trypanolytic, agglutinating and other protective bodies have been demonstrated. Carrying the analogy to syphilis we find that an individual may harbor spirochetes for forty or fifty years, while his skin and mucous membranes exhibit an insusceptibility to re-inoculation under natural exposure. However, as soon as he is freed from his infection he is again in as susceptible a state as he was prior to his first attack.

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It is a well-known clinical observation that after the development of the initial lesion a syphilitic is immune to a fresh infection. Why have the integument and mucous membranes ceased to react to organisms introduced from without when they are susceptible to their action from within? The opinion has been generally held that for infection to take place one of the first laws of its requirements is fulfilled by a surface covered by squamous epithelium. The earlier experiments on animals seemingly corroborated this view, for inoculations were only successful where scarification of a squamous-celled area was performed. Improved laboratory technique has, however, overcome the difficulty, positive results now being obtained in animals by the introduction of the virus into the testicle, peritoneal cavity, under the skin or directly into the circulation, especially the heart.

In human syphilis, while it is more usual for the general infection to be preceded by the development of a primary lesion, somewhere on the cutaneous or mucous surface, it is not rare for the local reaction to be altogether absent. To illustrate: a male nurse in my hospital service pricked himself with a needle used for obtaining blood for the Wassermann test directly after he had withdrawn it from the vein of a patient with florid syphilis. He was carefully watched for the development of a chancre at the site of injury, but the first macroscopic manifestation was a late secondary papule on his foot. Similar cases are reported in the literature. Another instance is exemplified in a personal communication by Dr. Dade, in which he related the infection of a young girl by blood transfusion. Her brother, whose blood was used for the treatment of her anemia, was at the time of the operation in the second incubation period of the disease. She in due course of time developed a secondary rash. Congenital lues is a further example of syphilis without the development of an initial lesion. Neisser came to the opinion, from his many experimental observations, that in certain cases infection might take place through the integument without visible or even microscopic changes, the organisms gaining access to the lymphatic or blood stream direct.

When spirochetes are successfully implanted, what takes place? As soon as they have become acclimated to changed nutritional conditions at the site of inoculation, as shown by Levaditi and Yamanouchi, they multiply, call forth microscopic changes in the cutaneous vessels, and enter the lymph and blood stream. This is known as the first incubation period and varies in length in different subjects. Just how far the organisms penetrate beyond the local sore and satellite lymph nodes in human subjects in this stage is not known, but it has been demonstrated by Neisser that the spleen and marrow of inoculated monkeys contain virus thus early in the infection. Now, as the chancre is forming a peculiar reaction on the part of the host is also developing. At first it is so feeble that the individual is for some time susceptible to re-inoculation. In animals it has been found that superinfection is possible if made eight days before the evolution of the primary lesion. Not rarely we see patients with multiple chancres. In some instances they develop simultaneously as the result of multiple inoculations; in others they appear successively either from auto-inoculation or contamination with a fresh virus. Human and animal experiments are at one in showing that superinfection lesions do not develop in the typical manner of those implanted on a virgin soil. Their incubation period is shorter and their clinical characteristics simulate those of the stage the patient is in at the time; that is, papular if close to the secondary period and ulcerative if in the tertiary stage. In other words, they are the expression of an altered tissue reaction. The hypothesis has been advanced by Krause and Volk that this immunity has a regional development, beginning at the site of the primary sore and progressively involving the mucous and cutaneous covering. Neisser has suggested that the susceptibility to re-infection returns in an inverse manner.

During the second incubation period the refractory state continues to develop until it attains its maximum with the outbreak of the secondary rash. Even now, however, it is only relative, for laboratory experiments have yielded positive results if special methods are employed, namely, larger amounts of active virus introduced subepidermically. From a clinical stand-point, however, this refractory state, or anergy—the term usually applied—is complete as far as ordinary infection is concerned, disappearing only with the cure of the disease, when the patient is again in a receptive condition.

It has been demonstrated further that the anergy is a specific one, the attempts of Neisser, Baermann, and Halberstädter to induce it by inoculation with Spirocheta pertenuis, of Hidaka with Spirocheta duttoni, and of Uhlenhuth with Trypanosoma lewisii having proved futile. None of these infections protected against that of syphilis, while, on the other hand, luetic animals were all susceptible to frambesia, relapsing fever, and dourine. Little is known of the nature of this state of resistance or how it is brought about, whether by the tissues, cells, the serum, or intermediary organs. Organisms or their toxins when introduced into the body behave as antigens and stimulate the formation of antibodies which are specific for that particular bacterium. These antibodies are of the nature of antitoxins which neutralize the toxins; opsonins which lead to the ingestion and destruction of the organisms by the leukocytes; agglutinins which cause the organisms to adhere together and probably also bring about their destruction and bacteriolysins which cause their dissolution. From the contributions to this branch of research in lues the conclusions are that substances of a parasiticide nature do not develop in the course of the disease. At the most, says Neisser, we can reckon with complement binding and agglutinating substances of a specific nature. Levaditi, however, argues that since the spirochetes even before the evolution of the primary lesion may penetrate to the hematopœtic organs, they act like true antigens and their products of secretion stimulate the formation of antibodies. He assumes an analogy between these immune bodies and those of related diseases, where bacteriotropic substances and opsonins ensure destruction by phagocytosis. *Pari passu* with this antibody formation the skin acquires a refractory state to exogenous spirochetes, the biological changes being sufficiently advanced at the close of the second incubation period to determine the character of the reaction. He has offered two attractive hypotheses to explain why the skin which is resistant to exogenous spirochetes reacts to endogenous organisms, (1) by a generalized eruption, and (2) after a varying latency, by local and destructive lesions. His assumption is that for a time the immune bodies hinder the multiplication of the parasite, but with the enfeeblement or disappearance of the former the virus gains the ascendency, generalizes itself, and produces the secondary eruption. Or the spirochetes are vaccinated, so to speak, against the immune bodies, and, becoming resistant to these defensive substances, they succeed in multiplying and provoking the exanthem.

It is a well-established clinical fact that the early cutaneous lesions are superficial and generalized, that with each relapse they show a tendency to localization and grouping with involvement of the deeper structures until we reach the tertiary stage with extensive destruction. Since it has been shown that these differences are not inherent in the specific virus but in the tissues of the host brought about by prolonged contact with the causal agent, the term allergy or, according to Neisser, Umstimmung has been proposed to explain the biological change which has taken place in the tissues. In the primary and secondary stage, when the organisms are numerous, the host is refractory; in the tertiary stage when they are few in number an anaphylactic state exists, the tissues are frail and more readily undergo necrosis. This is also seen in superinfection in tertiary syphilitics when the lesion corresponds to that type, and in the luetin reaction, which is especially applicable in congenital and tertiary syphilis, depending for its result on the hypersusceptibility of the tissues. In tuberculosis a similar condition is encountered. Erythema induratum, for instance, is caused by few organisms, and yet clinically presents extensive destructive lesions. Another clinical type is seen in large and deep ulcerations of the extremities in tuberculous subjects, all treatment, excepting surgical, being of little avail. The writer has recently had under his care a young man with glandular tuberculosis in whom the entire right leg was involved, necrosis extending through the musculature and laying bare the bone.

The immunity processes as outlined in the foregoing considerations are subject to modification under treatment. Where treatment is intensive and yet not sufficient to effect a complete cure it would appear that the anaphylactic stage is hastened, for it has been repeatedly claimed that specific remedies given early in the disease tend to produce relapses of severe local intensity. Herein we find the basis for the contention that salvarsan has changed the course of the disease, and when not given in sufficient doses to sterilize the patient, tertiary lesions appear much earlier than when the affection is permitted to run its course with the gradual establishment of a defensive mechanism, and consequently a longer refractory state. In so-called malignant syphilis we must also seek the cause in a precocious anaphylactic condition of the tissues rather than in the type of the invading organism, the reason usually evoked for this form of the infection. It has repeatedly been reported that spirochetes are numerically few in such lesions and that successful inoculations are relatively rare.

As accumulated evidence has shown that individual immunity is only relative, so racial immunity in the strict sense of the word does not exist. Lesser has said that neither race nor climate makes any difference in the receptivity of the virus of syphilis. Furthermore, it has been demonstrated that the children of syphilitic parents do not develop an immunity. Such children may be frankly syphilitic at the time of birth or they may be in the latent stage for years (syphilis hereditaria tardiva). Or if they escape infection and acquire the disease later on, it has never been observed to have a milder course. Gluck reports that although syphilization is almost general in Bosnia, extra-uterine acquired lues is not rare. He noted 10 per cent. of cases of recent syphilis in children under fifteen years, one-third of whom were only five or six months old.

While complete statistics and comparative studies on the course of the disease in the different races are not available, the investigations made have revealed some interesting facts. Neisser found that in the Malays primary and secondary syphilis was insignificant. Treatment is therefore deferred and the percentage of cutaneous tertiary manifestations is proportionately large. He seldom met with visceral or nerve manifestations, and never encountered tabes or paresis. In Java and the tropics generally Europeans suffer more severely than the natives, which is attributable to unfavorable climatic conditions and changed mode of living. According to Quennac, Europeans, Hindoos, and Arabs in Africa suffer severely while the negroes only have mild attacks. In Central America, Rutschuh reported severe syphilis in the whites and negroes in contradistinction to the Indians and half-breeds who only suffered mildly. Among the Indians in the United States the infection is very destructive in some localities, as cited by Dr. Hrdlička, while it runs a mild course in certain other tribes. This authority also states that he has never seen tabes or paresis among the Indians, although they suffer from other forms of mental disease. As to the negroes in our country the writer has a personal communication from Dr. Green, of Milledgeville, Georgia, in which the statistics collected by him show that 5.27 per cent. of negroes suffer from paresis as against 2.12 per cent. of whites. Tabes is rare in this race.

It is often said that the European pandemic at the end of the fifteenth century was an exceedingly malignant one. This claim is now challenged by syphilographers that the disease was malignant in the present sense of the word, that is, ulcerating lesions in the early secondary period, but rather that many of the so-called cases were ordinary ulcerating tertiary forms. Instead of malignancy *per se* and a racial susceptibility, other factors are called into account, as the undeveloped treatment, wars, famines, etc. Neisser suggests that spirochetes in their continual passage through human beings lose in virulence, or that the treatment which the patient receives so modifies the virulence that when such modified spirochetes are transmitted they produce a modified disease.

HEREDITY. The question of the transmission of syphilis to the offspring is a very complicated one, and still far from clear. While the accession of serological knowledge has presented a partial solution, there still remain certain clinical phenomena for which no satisfactory explanation can be given.

The opinion is gaining on almost every hand today that germinal infection on the side of the father does not take place, but that the mother, infected by the father either before or at the time of conception, transmits the disease to the fetus through the placenta. Is this view tenable on the ground of our clinical and laboratory observations?

Disease of the testicles during the secondary stage is not common, although it has been demonstrated by animal experiments that this organ is one of the seats of election of the syphilitic virus. Later a diffuse orchitis is more frequent, and during the tertiary stage gummata are not uncommon. As to other lesions of the genito-urinary tract which might harbor spirochetes little is known.

In the transmission of syphilis the results depend upon the intensity of the infection, which intensity weakens with time.

In the secondary stage it is most active, so that a man is almost certain to infect his wife. If she becomes pregnant early abortion will result. Such a woman, if untreated may abort later, then have a stillborn child or a living child with active syphilis, and finally, after eight to twelve to twenty years, healthy children. Such women are obviously syphilitic. On the other hand, there is the group of women who have been free from the clinical manifestations of the disease but who have had several miscarriages or children with unmistakable signs of the infection. These women, according to Colles-Baumès law, have not syphilis but are immune to syphilis. What has taken place that prevents such a woman from developing a primary sore or a secondary rash and still has rendered her insusceptible to the disease? Is it because she has the infection or because Wassermann substances or antibodies are passed through the placenta? In other words, must we conclude in view of the positive Wassermann reaction that her tissues are harboring living spirochetes which without treatment are overcome by the defensive mechanism of the patient or does she simply receive Wassermann-producing substances?

Serological research has in the main overthrown Colles' and Profeta's laws. It has been demonstrated by a host of investigators that the majority of women apparently healthy who give birth to syphilitic children have a positive Wassermann reaction and are therefore in the latent stage of the disease. Furthermore, Baisch, Trinchese, and Weber constantly found spirochetes in the maternal portion of the placenta and in the intervillous spaces even in negatively reacting women. The claim then that Wassermann-producing substances pass over from the fetus to the mother had to be dismissed as the persistence of the reaction after birth was strong presumptive evidence of the presence of living spirochetes, their demonstration in the placenta supporting the contention. The transmission of organisms to the fetus by way of the placenta finds its analogy in other diseases, such as smallpox, relapsing fever, and tuberculosis. In tuberculosis this takes place only in advanced and florid cases in contradistinction to lues, where no clinical evidence of the disease may be present, multiplication of the spirochetes probably taking place through the impetus given by pregnancy. It is interesting to note in passing that Uhlenhuth found typical testicular lesions in the young of a syphilitic mother rabbit, illustrating that the organisms pass through the placenta. Varying degrees of latency are met with. In some women a negative Wassermann in the blood is accompanied by a positive reaction in the colostrum of the breast, or the placental blood may be stronger than the rest of the serum. The evidence submitted in favor of maternal transmission is convincing, but the question as to how the mother received her infection is not so easy of solution. Is she inoculated prior to or at the time of conception or later? Do the organisms penetrate the ovum or do they enter the tissues of the mother without the production of the usual sequence of symptoms? It has been shown experimentally that the semen of latent syphilitic men may from time to time contain spirochetes. As many of these patients have had more or less treatment, it has been suggested that an attenuated form of the disease is transmitted to the wife. There are two ways in which paternal transmission could take place. In the one we may assume that the parasite is carried in the head of the spermatozoön and with it penetrates the ovum. .As the organism is three times the length of the spermhead this possibility is dismissed by the majority of syphilographers. The other alternative is that the spirochetes are free in the semen and with it enter the egg cell. Such an event it is believed would have an untoward effect on the fertilized ovum, as it has been shown that the disturbance of a single blastomere in lower vertebrates is sufficient to arrest development or cause malformation, and the regenerative powers are greater in these animals than in the higher vertebrates (Weber).

LATENCY. What is our present conception of latency in syphilis? During these periods of apparent quiescence does the defensive mechanism hold the pathogenic agent in abeyance or is some pathological process insidiously undermining tissue in some part of the body? The application of the Wassermann reaction has materially changed our views since the demonstration in a large number of so-called latent syphilitics of involvement of the aorta and the central nervous system. It has been shown that such patients may have a chronic meningitis for years without producing obstrusive symptoms, and a limited aortitis may persist for a long time without making its presence known either subjectively or objectively. Aside from gummatous involvement of the viscera little is known of the effects of the infection on the various organs. Where must we seek the explanation of persistent Wassermann reactions in cases intensively treated in whom involvement of the central nervous system and the heart and aorta can be excluded? A solution will probably be reached when the nature of the Wassermann reaction is fathomed, but on *a priori* grounds if a focus in the aorta or nervous system is capable of keeping up a positive reaction indefinitely, it is reasonable to assume that a similar process in one of the viscera may be provocative of a like result.

It is often asked where the spirochetes are lodged during the latent period. A number of investigators have urged that during this stage, resting forms of the organisms are harbored by the lymph nodes or blood-forming organs. Present knowledge does not support the theory of a cycle of evolution with the power to produce lesions according to the stage of its development. Spirochetes recovered from any source whatever—chancre, mucous patch, or gumma—the blood, nervous system, or viscera have all shown similar morphological and practically the same biological characteristics.

The relation of trauma to the localization of specific lesions has been so well appreciated by the medical profession that it is given a prominent place as an etiological factor. The query naturally arises as to whether the spirochetes in such cases have remained *in loco* since their primary deposition or are carried there by the blood after injury to the tissue. Pasini found spirochetes in an atropic and pigmented spot two years after the involution of a papular syphilide, while Hoffman demonstrated them in scar tissue of chancres long after their regression. Levaditi and Yamanouchi were able to recover them from the cornea of a rabbit one hundred and thirteen days after the keratitis had healed and at which time a recurrence took place. The so-called chancre redux is interpreted by many as the result of organisms which have escaped destruction rather than as a superinfection with a new strain. Neisser has demonstrated that spirochetes may be present in the skin without producing any macroscopic changes, and more recently Whartin has called attention to their presence in the heart without exciting tissue reaction.

Studies on the infectiousness of the blood in the various stages of syphilis have supplied us with the following data: In 19 cases of primary syphilis, Uhlenhuth and Mulzer obtained positive results in 16 rabbits injected with 2 c.c. of defibrinated blood into the testicle; in 36 cases of early secondary syphilis, 27 positive results, and in 15 cases of latent syphilis 2 successful inoculations. One of the latter was with the blood from a woman whose infection was four years old and who eighteen days before had given birth to a syphilitic child. Lieberman also succeeded with the blood from a woman whose primary lesion dated back four years and who six weeks before had given birth to a luetic child. Frühwald reports 2 cases: In one the disease had existed for one year, the Wassermann was positive and the patient had had two doses of neosalvarsan, each 0.75 gm.; in the other the infection was one and a half years old, the Wassermann was positive, and the patient had received two doses of neosalvarsan of 0.6 gm. each.

Numerous attempts have been made with the blood of paretics and tabetics, but with little success. Levaditi demonstrated spirochetes in the blood of one patient with paresis, and Graves reported positive results with blood from two paretics. Ellis' experiments to confirm these findings gave constantly negative results.

The above facts are in accord with the clinical teaching that the blood of luetic individuals is infectious during the active primary and secondary stage, and that this diminishes with the age of the disease. Exceptions to the innocuousness of the blood of latent syphilitics are seen in the occasional infection of a surgeon in his operative work on an individual in this period of the disease. It is to be inferred therefore from clinical and laboratory experience that under conditions of which we are at present ignorant, spirochetes may reach the circulation from some focus in the body. In certain cases this may precede the cutaneous relapse, in others it is accompanied by no visible manifestations. Kraus has called attention to febrile attacks as the only symptom of latent lues, and suggests the spirochetemia as a possible explanation. An analogy is found in trypanosomiasis where the parasites may disappear spontaneously from the blood and reappearing give rise to an eruption and fever. Moreover, a latent period of three years may ensue before the nervous symptoms appear.

PATHOLOGICAL ANATOMY. The predilection of syphilis for the vascular system is noted almost from the inception of the disease in the involvement of the cutaneous vessels at the point of inoculation. Here the pathological process consists of an endarteritis, later a panarteritis, with a characteristic inflammatory infiltration. Excepting the macule all the lesions succeeding the chancre show a marked affection of the vessels, especially those of the late secondary and tertiary stages. The formation of giant cells so frequently encountered in the secondary papule, the nodular syphilide and gumma may be traced to a vascular genesis, while the extension of serpigenous lesions may be explained by the progressive thrombosis of the vessels.

A study of the pathological anatomy of syphilis shows that fundamentally the reaction is on the part of the fixed connective-tissue elements, the labile constituents coming into play locally only secondarily. The chief cells are the lymphocyte and the plasma cell, the latter believed to be a derivative of the former and the antecedent of the fibroblast. It has been shown by Hazen that a circulatory leukocytosis is present in untreated secondary cases, sometimes as high as 20,000 white cells. The neutrophiles are absolutely and relatively increased and the percentage of eosinophiles is higher.

Under treatment there is a slight drop in the total count, with a marked relative increase in lymphocytes which under treatment may run as high as 65 per cent.

The syphilitic process is essentially a granuloma having its origin in the perivascular lymphatic spaces. In the primary lesion the main changes are found in the cutis, the very earliest of which are in the new formation of capillaries and the grouping about these and preëxisting vessels of lymphocytes and plasma cells. At first they mantle the vascular structures as a "coat-sleeve" infiltration, but as the lesion grows older, spread out and become diffuse. The endothelium of the capillaries is swollen and proliferated so that the lumen is narrowed or altogether occluded, and in the larger vessels with an external coat there is in addition evidence of inflammation and an increase in thickness. In some instances giant cells are found. From the newly formed granulation tissue, connective tissue is formed which later scleroses and leads to induration. Owing to interference with nutrition, regressive metamorphosis sets in. The epidermis presents a varied picture, depending on whether there is pressure from the infiltrate or retrograde changes with erosion and ulceration.

In the secondary stage the disease is characterized by a succession of eruptions and a general adenopathy. Ehrmann has said that the distribution of secondary syphilides is governed by the branching of the vascular stems. The roseola or macular syphilide under the microscope shows very few changes, being simply an erythema with dilatation of the vessels of the papillary body and adjoining corium and an infiltration of lymphocytes and plasma cells about them. In the papular or lenticular syphilide we find in the cutis a circumscribed lesion made up of lymphocytes, plasma cells, and proliferated fibroblasts, all in close relation with the vessels which show the characteristic changes. Lichen syphiliticus owes its peculiar features to localization, namely, distribution about the pilo-sebaceous apparatus. Here the process surrounds a hair follicle and extends deeply into the corium. Its structure is like that of other lesions, with usually abundant giant cells of vascular origin. The epidermis in all lesions of this stage shows only secondary changes. It may be thinned from pressure of the granulomatous tissue beneath or there may be edema with an increase in thickness and scaling. In condylomata papillomatous overgrowth is a marked feature. Pustular and suppurating syphilides usually signify extraneous inoculation with pus-producing organisms. The pigmentary syphilide, or leukoderma syphiliticum, according to Ehrmann, is due to chromatophores, the pigment passing from them to the basal layer of the epidermis.

As a rule, secondary syphilides undergo spontaneous absorption. Microscopic residua may, however, persist for a long time. Their connection with local relapses has been suggested.

The type of lesion of the tertiary period is the gumma. The process consists of an infiltration of lymphocytes, plasma cells, and proliferated connective-tissue cells about the vessels, newly formed and old, which are the seat of an endarteritis and panarteritis, and give rise to giant cells. Caseous degeneration usually begins in the centre of the granuloma, or in some cases it may be fatty or mucoid in character. The last mentioned is most often found in bones. The necrotic areas liquefy and are absorbed or discharged, the usual procedure being gradual absorption, with formation of cicatricial tissue, the contraction of which leads to deformity. It is believed by many that the fibrosis is not purely a process of repair or due to the irritating action of necrotic tissue, but that there is also a syphilitic element. The plasma cell thought to be the precursor of the fibroblast has been credited with being more than a passive participant. The late nodular or tubercular syphilide is in reality a gumma, situated more superficially in the cutis. The serpigenous lesions which also belong to this stage are made up of groups of nodules situated about the cutaneous vessels, the thrombosis of which probably explains the progressive character of the lesion.

Syphilitic phlebitis is relatively infrequent, occurs usually in the veins of the lower extremities, and is of minor importance. Arterial disease, however, is very common and of serious import, the vessels especially attacked being the aorta, the cerebral, pulmonary, subclavian, femoral, and popliteal arteries. Owing to disease of the walls, vasomotor response is impaired or lost, and where there are obliterative changes due to endothelial proliferation or secondary thrombosis, interference with the blood supply and impairment of nutrition. While the brain and the heart suffer more severely in this respect, other organs and the vessels of the extremities are not exempt. Several years ago the writer had under observation a case of gangrene of the leg consecutive to a syphilitic thrombosis of the femoral artery (Fig. 1). The patient was a colored girl, in the City Hospital, upon whom several amputations were made, after each of which the gangrenous process developed and spread. A picture closely simulating Raynaud's disease is also met with as the result of luetic involvement of the vascular supply of the extremities, and in several cases of symmetrical cutaneous atrophy which I have had under my care the syphilitic element was the predominant feature.

AORTITIS. It is only within the last decennium that the syphilogenic nature of aortitis or mesaortitis has been generally recognized among internists and syphilographers. During this period the development of the Wassermann reaction and roentgenology, as supplementary to the physical examination, have shown us how widely prevalent the disease is among individuals who have had a syphilitic infection.

As to its frequency of incidence, Chiari found the condition present in 59 per cent., Fahr in 29 per cent., and Fraenkel fifty-three times in 102 cases of constitutional syphilis. Stadler, whose statistics cover 256 cases, demonstrated the disease in 82 per cent., and of 211 of this number it was the cause of death in 117. Staub found an aortitis in 82 per cent. of paretics which came to autopsy, Buder in 84.5 per cent., and Alzheimer in 74 per cent. The findings of Rach and Wiesner show that in congenital syphilis, changes in the aorta or pulmonary artery are seen in 67.4 per cent. Lenz states that in large cities 25 per cent. of all syphilitics die from aortitis (angina pectoris, aortitic insufficiency, aneurysm) as against 3 to 4 per cent. from paresis, 1 to 2 per cent. from tabes, and 10 per cent. from all other syphilitic affections, as of the brain, liver, kidneys, etc.

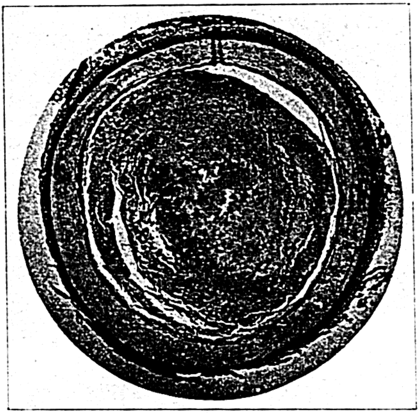

FIG. 1.—Syphilitic thrombosis of femoral artery. Transverse section of artery, showing thrombus and thickening of arterial coats.

Mesaortitis has been defined by Doehle, Heller, and others as a specific inflammation of the adventitia and media which terminates in cicatricial deformity. As a rule, there is a combination of processes so that cicatrization may be present in one part while active inflammatory lesions are found in another. The disease shows a decided preference for the ascending portion of the aorta and the arch, the explanation being that the impact of the blood is greater here than in the rest of its extent, following the well-known law that syphilis localizes where trauma has produced a *locus minoris resistentiæ*. In contradistinction, atheroma selects the lower portion of the aorta where the mechanical element is of slighter moment. Stadler could find no relationship between an increased blood-pressure or marked variations in pressure. Strümpell favors a summation of injurious agencies, as the noxious influence of alcohol and tobacco, with consequent lowering of resistance of the vessels.

Grossly the aorta gives a characteristic picture (Fig. 2). The inner surface shows isolated or confluent elevated, wrinkled, grayish, and translucent sclerous areas, with puckering or cicatricial pitting, or again radiating ridges with depressed cicatrices between. The intima over the affected areas preserves its glistening appearance. The thickness of the artery varies in different portions, so that while indurated and sclerotic at one point it is thin and translucent at another. Depending on the extent of involvement, dilatation is present. This may be uniform throughout the length of the thoracic portion or appear as small aneurysmal pouchings or a true saccular aneurysm. All transitions are found. Ordinarily it is not difficult to differentiate this condition from arteriosclerosis in the absence of fatty degeneration and calcification. However, in old subjects there may be a combination.

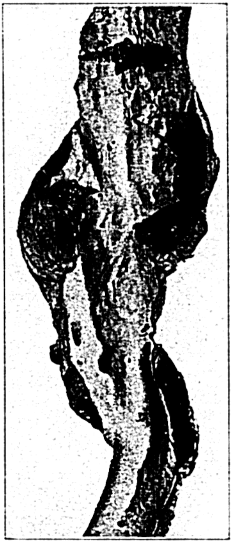

FIG. 2.—Syphilitic aortitis, showing characteristic changes in the walls of the vessels, transverse rupture, and dissecting aneurysm into coats of the aorta. (Specimen of Dr. John H. Larkin.)

In the beginning the lesion is often confined to the vessel in proximity to the aortic valves. Later it extends to them and gives rise to insufficiency, which condition is very frequent. With the extension of the process the ascending aorta and the arch are involved. Not rarely changes are also noted about the mouths of the larger branches of the arch, causing narrowing of the left carotid, innominate, and subclavian arteries, which localization is significant from a clinical point of view. With involvement of the aortic ring the mouths of the coronary arteries are also considerably reduced.

The relation of syphilis to aortitis was for a long time disputed. On the one hand investigators classed it with parasyphilis because of the difficulty of demonstrating spirochetes, its indurative or fibrotic tendencies, and indifferent results from treatment. On the other, which has the support of recent examinations, it was classed with active syphilis. The demonstration of spirochetes in the aortic wall by Reuter, Schmorl, Wright, Richardson, and others in acquired syphilis, and by Wiesner and Rach in congenital, together with the microscopic picture of gummatous lesions, and a positive Wassermann reaction in about 80 per cent. of cases, definitely places the affection in the category of active syphilis. It is difficult to demonstrate the organisms even in comparatively recent and active lesions. This, however, does not militate against their syphilitic nature, as they are equally difficult to demonstrate in cutaneous gummata. In both the tissue is probably in a state of altered reactivity, so that numerically few organisms are capable of bringing about the necrotic change. The striking changes are in the media, although the disease begins in the adventitia. Miliary gummata undergo necrosis and are replaced by cicatricial tissue. In the adventitia in recent processes an inflammatory infiltrate of lymphocytes and plasma cells is localized about the vasa vasorum (Fig. 3), while in older ones only fibrotic changes may be left (Fig. 4), the nutrient vessels themselves being the seat of an obliterating endarteritis, such as is found in syphilitic lesions elsewhere in the body. The elastic tissue, and this is characteristic of luetic disease

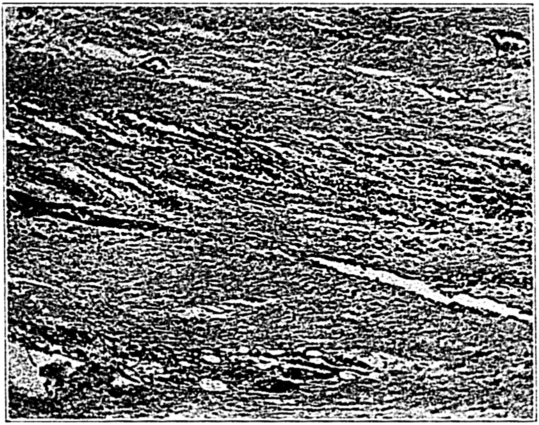

FIG. 3.—Early stage of aortitis, showing characteristic lymphocytic and plasma-cell infiltration about the small vessels in the adventitia.

of the larger vessels, is either fragmented or has entirely disappeared. The intima shows no change at all or various grades of a compensatory thickening. On the question of genesis of the early changes there is some dissonance of opinion. Doehle, Heller, Backhaus, Saathoff, and others trace the beginning of the disease to the vasa vasorum. They claim, primarily, a swelling of the endothelium of these vessels in the middle third of the media to large epitheloid cells, which lead to an obliteration with secondary regressive metamorphosis of the aortic wall. Marchand, Beneke, Arnsperger, and others not corroborating these findings incline to the view that the medial changes are primary, the virus so injuring the elastic lamellæ that they succumb to the pressure of the blood. The difficulty of determining the genesis with positiveness even early is apparent, for, as Stadler points out, a simple infiltration of the vasa vasorum may also occur under the influence of the toxins of alcohol and other infections. Benda describes two forms of aortic disease. In the one submiliary lesions without necrosis which cicatrize and leave none or only a very slight deformity of the vessel wall, in the other typical gummata, with central necrosis, the scarring of which leads to typical sclerotic changes in the wall.

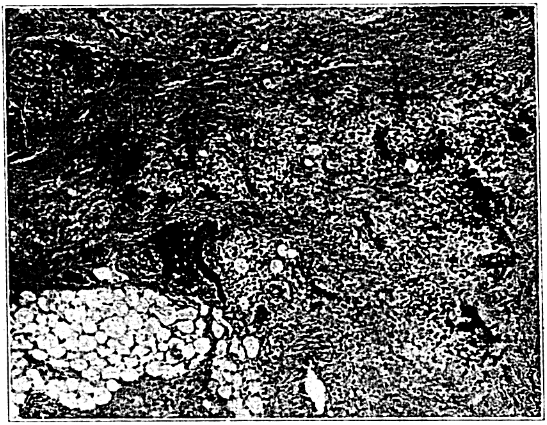

FIG. 4.—Later stage of aortitis, showing advanced sclerosis of the vessel walls.

The clinical diagnosis of aortitis is often extremely difficult. Limited and circumscribed changes of the ascending portion without involvement of the ring are, as a rule, not accompanied by subjective or objective manifestations. Such patients may be observed for a long time without eliciting signs pointing to the condition. Roentgen-ray examination also being negative. Only when a greater area is involved especially more or less of the circumference are there symptoms suggestive of disease, namely, pain, dyspnea, and tachycardia on slight exertion, increased blood-pressure, weakness, and easily induced fatigue.

The pain is often the primary and predominant symptom, although frequently it is lacking or indefinite. It is characterized as a dull aching or a feeling of pressure under the sternum, with pain radiating to the side of the chest, the back, and the arms. Disease of the innominate, carotid, and subclavian may be attended by a condition simulating intermittent claudication of the lower extremities, with weakness, radiating pain, and sensory disturbance. Periodic or continuous headaches, often with vertigo, accompany involvement of the mouth of the left carotid, and where the coronary arteries are the seat of disease the attacks are anginal in character. There appears to be no satisfactory explanation for the origin of the pain. Thoma referred it to injury of the larger and smaller nerve trunks as well as irritation of the Pacinian bodies in the aortic wall. Huchard attributes it to a peri-aortitis, and the neuralgic pains in the chest and shoulder to the changed relation of the subclavian to the brachial plexus. Longcope came to the conclusion that the anginal attacks were due to reflex disturbances set up by the syphilitic process involving the root of the aorta, the paroxysmal dyspnea being regarded as an acute bronchiospasm.

When does the aortic disease begin? Obviously this is difficult to affirm, as the disease in the majority of cases is insidious in its onset, the first symptoms appearing only when the affection has made some progress. In assuming that involvement takes place at the close of the primary stage when there is a general dissemination of the spirochetes, we are confronted with the same problem as when we endeavor to establish the time of infection of the central nervous system. Palpitation, arrhythmia, tachycardia, and disturbances in the pulse rate frequently occur in early secondary syphilis, which has been adduced as evidence that involvement takes place at the time the disease is a spirochetemia. The publication of fatal cases shortly after infection also inclines to the view that involvement takes place early. Brooks recorded perforation of an aneurysm before the secondary rash had fully appeared, and another case with a fatal aortic lesion within six months of infection. Longcope cites two patients who died from the effects of syphilitic aortitis four years after the appearance of the chancre. Stadler publishes two cases in whom death occurred five years after infection. The first patient, aged twenty-nine years, showed at autopsy a fibrous aortitis and aneurysm. The second, aged twenty-seven years, the objective and subjective signs of an aortitis.

He further studied 12 postmortem cases of severe secondary and tertiary syphilis in patients under thirty years of age. He assumed on account of the youth of the subjects that the infection could not have been of long standing, but in none were changes of syphilitic aortitis demonstrable.

The writer has recently investigated, in his private practice, all latent syphilitics, especially those with a persistent positive Wassermann, for the occurrence of cardiovascular disease, and in a large percentage has found the existence of such a lesion.

The average age at which the disease appears is forty-seven to forty-nine years, but it is not rare to find it in much younger patients. Aortic disease in general makes slow progress, for Weintraud, Stadler, and others give the average lapse of time as twenty years, the interval vacillating between five and forty years. The disease usually runs a fatal course in about two years after the development of the symptoms. The importance of early diagnosis is, therefore, apparent, especially in view of the fact that the affection is a manifestation of active syphilis and amenable to treatment. In 95 cases of aortitis collected by Benda the termination was as follows: In 9, coronary stenosis; in 22, aortic insufficiency; in 37, combined coronary stenosis and aortic insufficiency; in 27, aneurysm. In a total of 248 cases he found aneurysm forty-eight times.

The relation of cardiovascular affections to tabes has for a long time occupied the attention of clinicians. According to Lesser's statistics in 96 cases of tabes come to autopsy, aneurysm of the aorta was found eighteen times. A review of the literature shows that the coincidence of tabes and aortic insufficiency is most frequent. Rogge and Ruttner report the association in 6.5 per cent.; Rogge and Müller in 10 per cent.; Stintzing in 3.8 per cent., and Stadler in 6.2 per cent. of all cases of well-developed tabes. The latter did not include his cases of incipient tabes; in manifest tabes which came to autopsy, however, he found disease of the aorta in almost all. Rogge and Müller have called attention to the cause of sudden deaths in tabetics as being due to lesions referable to the central nervous system but to sudden cardiac insufficiency or rupture of an aneurysm. The so-called cardiac crises are in reality attacks of angina pectoris, due to changes in the coronary arteries.

Strümpell has emphasized the surprisingly frequent presence of rudimentary tabes in patients who seek medical advice for symptoms referable to the heart. Many of these cases show only pupillary changes, such as narrowing, irregularity, and fixation to light. Only one pupil may be affected, as in a case cited by him with severe endocarditis, myocarditis, and aortic insufficiency. The reflexes are only slightly altered or the Achilles reflex alone lost and the patellar reflex exaggerated. Observing these cases over a long period of time, weakening and gradual disappearance of the reflex may be noted. In general, symptoms of aortic disease appear later than the earliest tabetic manifestations. Rogge and Müller are of the opinion that tabetic symptoms average four and a half years earlier than those of the circulatory apparatus. It is probable that it is not a later involvement, only that the condition has a longer latency and therefore manifests itself later.

The writer has under treatment at the present time several patients with tabes and concomitant aortitis. One of them, with optic atrophy, has an aneurysm. Five others, in whom the tabetic symptoms have existed on an average of eight years, show a marked sclerosis of the aorta. In a paretic, Roentgen-ray examination shows dilatation of the ascending aorta and in a case of cerebrospinal syphilis, with cardiac symptoms developing four months ago, a small aneurysm. In another patient, aged thirty-one years, who had had an attack of hemiplegia four years ago, signs of aortitis have developed within the past few months. The Roentgen-ray plate also show a marked sclerosis.

For the following interesting postmortem examination and also some of the illustrations which accompany this article I am indebted to Dr. John H. Larkin, Director of Pathological Laboratories, Department of Charities, New York City:

J. E., aged forty years. The patient was admitted to the City Hospital (service of Dr. Evan Evans) the latter part of 1913 for sciatica. After a few weeks he was discharged and five months later re-admitted, at which time in addition to the sciatic pains he complained of girdle pains. Lumbar puncture showed thirty-eight cells, an excess of globulin, and a strongly positive Wassermann. His serum was also positive. A diagnosis of tabes without clinical evidence, excepting the girdle pains, was made. Further examination, including Roentgen-rays, revealed an aneurysm of the ascending aorta. He was placed on salvarsan and mercurial treatment, which reduced his cell count and reversed the Wassermann in the fluid, but had no effect on that of the blood. The patient died suddenly from a rupture of the aneurysm into the thoracic cavity. Microscopically the aorta showed a characteristic picture with a round-celled infiltration in the adventitia. The interesting feature of the findings in this case was in the cord, which showed an involvement of the pia-arachnoid with a round-celled infiltration about the small vessels and an insular degeneration of the posterior nerve roots (Fig. 5). The posterior columns were unaffected.

NERVOUS SYSTEM. With the acquisition of more exact knowledge our ideas concerning syphilis of the nervous system have undergone considerable revision. The present views based on clinical and laboratory investigations may be formulated as follows: Infection of the central nervous system probably takes place in the early stage of the disease with the generalization of the virus. Accumulated clinical evidence points to meningeal involvement during the first few months, in some cases before the appearance of the cutaneous eruption. Lumbar puncture in the hands of different investigators has elicited varying results. Thus, Ravaut found the spinal fluid in secondary syphilis abnormal in 67 per cent. of cases, Altmann and Dreyfus in 78 per cent., Nonne in 40 per cent., and Swift and Ellis in 36 per cent. The writer's findings, based on the examination of cases in the secondary stage with and without cutaneous lesions, showed meningeal involvement in less than 20 per cent. Fournier's dictum that patients in whom secondary symptoms are overlooked or very mild later show involvement of the central nervous system has been reiterated again and again. This led Finger to divide syphilitics into two classes: those with manifest cutaneous lesions, and those with absent or mild skin lesions and meningeal involvement, which division is too arbitrary for many cases with severe cutaneous lesions as well as those which have been treated early later develop disease of the nervous system. The observation of patients over long periods of time has shown that a low-grade meningitis may exist for years without producing obtrusive nervous symptoms. Such lesions are comparable to the superficial lingual and palmar syphilides, which persist for years, produce little inconvenience, and are refractory to treatment. There has been a good deal of speculation as to whether the spirochetes producing lesions in the central nervous system are the remains of

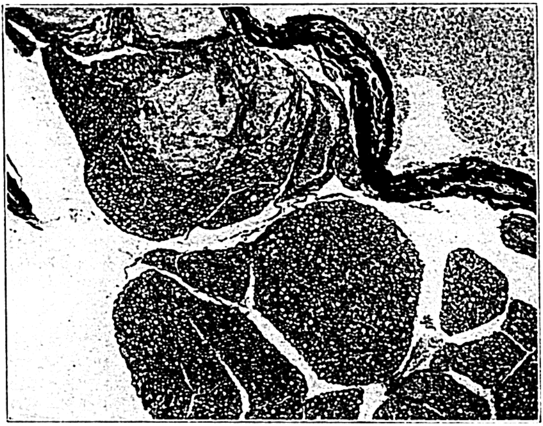

FIG. 5.—Insular sclerosis posterior nerve root, with accompanying meningitis. Posterior columns not involved.

those deposited during the spirochetemia or whether they later reach the nervous system from another focus. Head's work is perhaps suggestive. In seeking to explain the more frequent involvement of some areas in root affections over others he found that the roots most commonly subjected to irritation were those in connection by their visceral afferent fibers with certain organs known to be the seat of active spirochetosis in syphilis. Thus the second and third cervical contain afferent paths from the tonsil; the first, second, third, and fourth thoracic from the aorta, while those from the seventh thoracic to the first lumbar, the most frequently involved, carry afferent paths from the liver, kidney, suprarenal, and testicle, organs which are the sites of election of the parasite. Orr and Rows have shown in their investigations on the lymphogenous infection of the nervous system that organisms and their toxins travel along the perineural lymphatic space which surrounds every spinal nerve and extends along the roots to the pia mater. These spaces are not only in connection with the pia, but through the latter in communication with the adventitial lymph spaces of the perforating vessels. The rôle of these channels as distributors is therefore quite obvious.

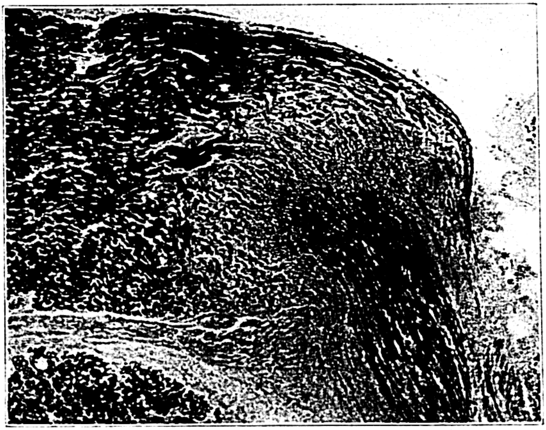

FIG. 6.—Degenerated posterior nerve root in tabes. Posterior columns involved.

The sharp distinction formerly drawn by clinicians and laboratory workers between cerebrospinal syphilis and parasyphilis is no longer tenable. Gradually the barrier has given way until we have come to regard these conditions as identical from an etiological stand-point, though differing in reaction, which difference depends on localization and the tissue involved. By cerebrospinal syphilis

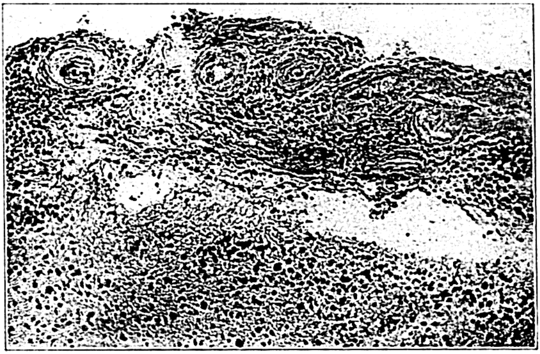

FIG. 7.—Syphilitic meningitis, showing various stages of obliterating endarteritis.

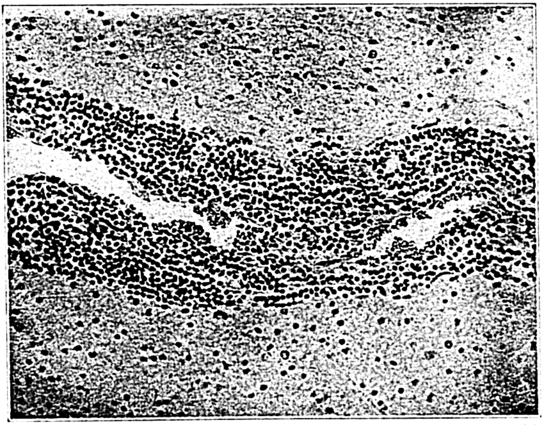

FIG. 8.—Mantling infiltration of lymphocytes and plasma cells about pial vessel in brain cortex.

we understand the exudative, vascular, and gummatous processes which involve the coverings of the nervous system and the bloodvessels within them (Figs. 7, 8, 9 and 10). These processes in the

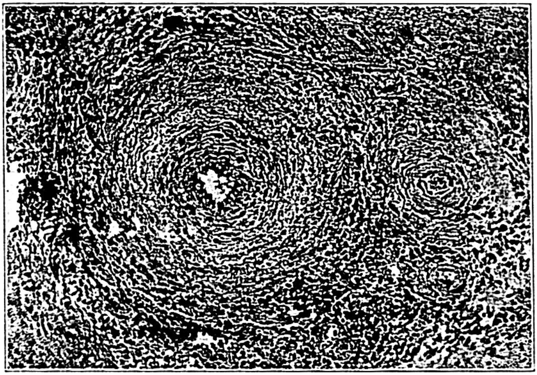

FIG. 9.—Heubner type of obliterating endarteritis in syphilitic meningitis.

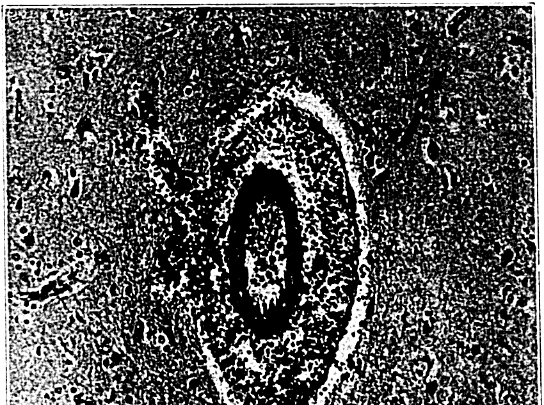

FIG. 10.—Small vessel in cortex of the brain, showing infiltration of perivascular spaces with lymphocytes and plasma cells.

great majority of cases remain superficial, but in some cases extend into the essential nervous structures along the pial or advential sheaths of the vessels, and give rise to the borderline cases of tabes and paresis.

It is proposed by Head and Fearnsides to divide luetic disease of the central nervous system into syphilis meningovascularis and syphilis centralis, the latter including all those cases where degeneration of nerve tracts or nuclei shows that the lesion must lie within the structure of the nervous system itself. As meningitis and endarteritis, however, are common to all these pathological states, this classification does not seem to the writer a tenable one.

What is the nature of paresis and tabes? In paresis there is a combined meningitis and encephalitis with a typical infiltration of lymphocytes and plasma cells in the adventitial lymph spaces (Figs. 11 and 12), the secondary degenerative changes probably depending on the primary vascular disease. Likewise we have a meningitis in tabes, but it is easier to comprehend the pathological condition and manner of invasion in paresis than the tract degeneration in the cord. The view that the genesis of both affections lies in a chronic meningitis now has a pretty wide acceptance. In tabes, Nonne believes it leads to disease of the roots and secondarily of the posterior columns. Nageotte was the first, in 1894, to describe a low-grade meningitis at the junction of the anterior and posterior roots on the proximal side of the ganglion, and in addition a neuritis, as shown by an inflammatory condition in the perineurium and a perivascular infiltration of plasma cells and lymphocytes in the posterior roots. This was confirmed by Dinkler, Dejerine, and others, but their views were not generally accepted, as the findings were interpreted as a combination. Again, in 1906, Schröder showed that collections of lymphocytes and plasma cells occur in the lymph spaces of the vessels in paresis and tabes, and that in the latter they are found not only in the pia and connective tissue about the vessels in the peripheral parts of the cord, but in the intramedullary portion of the columns as well.

Stargardt's findings in optic neuritis also have an important bearing. In a number of cases of tabes and paresis he found a true inflammation of the sheath and endoneurium. He also described an active inflammatory process in the joint structures of tabetic arthropathy, as evidenced by plasma cells and lymphocytes, with endarteritis of the small vessels. Steiner's studies on peripheral nerves in tabes and paresis also brought him to the conclusion that the process is an inflammatory one. The older view of a primary neuron degeneration in the light of present evidence would seem to have to be abandoned.

According to McIntosh, Fildes, Head, and Fearnsides, parasyphilis "depends upon an anaphylactic reaction in the tissues of the central nervous system which have been rendered hypersensi-

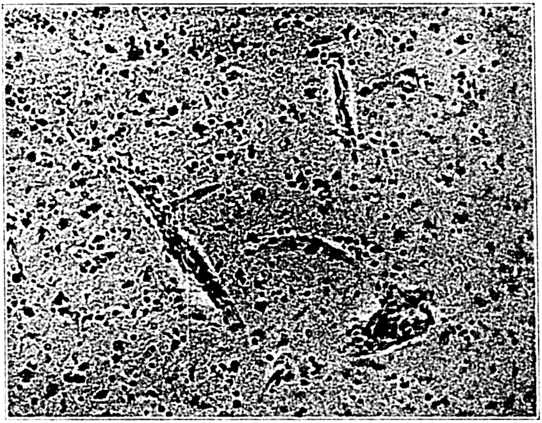

Fig. 11.—Showing the characteristic picture of paresis, with plasma-cell infiltration.

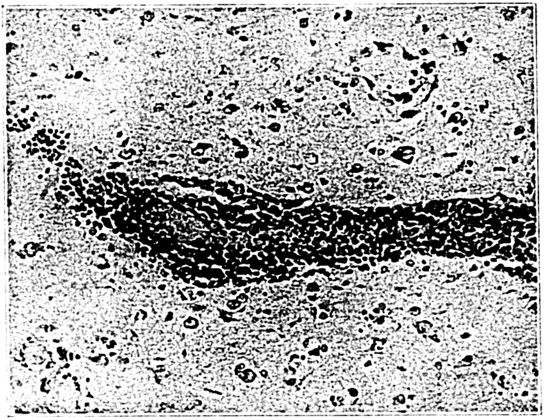

Fig. 12.—Paresis, showing the grouping of lymphocytes and plasma-cells about small vessels in cerebral cortex.

tive in accordance with their peculiar lymphatic distribution." Since it has been shown by Marie and Guillain, Orr and Rows, and others that the posterior columns are in direct lymphatic communication with the posterior roots, the aforementioned authors have evolved the theory that sensitization takes place during the secondary period by the spirochetes or their toxins ascending the afferent peripheral nerves. When spirochetes again become active in the posterior columns a violent reaction may ensue, injuring the nerve fibers and producing proliferation of the neuroglia and wandering cells. The injury of the nerve fibers will lead to degeneration, which will continue as far as the reflexion of the neurilemma. In the same way the cerebrum or isolated groups of cells in the anterior horns or other groups of fibers or cells alone or in combination may be affected, the particular region involved determining the clinical picture. Noguchi had previously shown by animal experiments that sensitization may be necessary before spirochetes can infect the brain. In both rabbits and monkeys he obtained negative results when the organisms were inoculated directly into the brain. He therefore injected rabbits with living and dead spirochetes intravenously, and after five months inoculated them subdurally with a particle of a scrotal syphiloma rich in spirochetes. They all remained well for two months, then became emaciated, and showed a slightly ataxic and spastic gait. The symptoms continued to increase, and after five months the animals were no longer able to jump. Microscopically some of these animals showed identical changes, with paresis, but the nerve cells were intact. In three an exudative meningitis was found and in one a unilateral atrophy of the frontal lobe. The control animals without previous sensitization remained well.

Analogies are frequently drawn between tabes and paresis and sleeping sickness. Spielmeyer, as the result of extensive investigations, came to the conclusion that in incipient cases the diagnosis between paresis and trypanosomiasis is not possible. He was able to produce in dogs with Trypanosma brucei an involvement of the central nervous system which was like human tabes. After nine to ten weeks the process was found in the posterior roots with beginning extension to the posterior columns, sensory trigeminus, and optic nerve. In trypanosomiasis, however, the central nervous system rarely escapes, whereas in syphilis only 1 or 2 per cent. develop tabes and 4 to 5 per cent. paresis.

CONCLUSIONS: Clinical observation and experimental work have shown that no true immunity exists in syphilis, but that an anergy develops during the first incubation period and is complete at the time of the general eruption. This refractory state usually persists as long as the body harbors spirochetes, and when it disappears, with the cure of the disease, the patient is again in a receptive state.

In the transmission of syphilis to the offspring the theory of spermatic infection has been abandoned in favor of placental infection, as the majority of mothers of congenitally syphilitic children have a positive Wassermann or show spirochetes in the intervillous spaces and maternal portion of the placenta.

The histopathology of syphilis is a uniform one. In all stages and in all organs the lesion begins in the perivascular lymph spaces as a lymphocytic and plasma-cell infiltration. The distribution of secondary lesions, according to Ehrmann, is due to a branching of the vascular stems. In the tertiary stage the ulcerative and destructive character of the lesions finds its explanation in a changed tissue reaction, the Umstimmung of Neisser, or allergy, in the sense of an increased susceptibility to the action of the organisms.

Syphilis produces a characteristic type of aortitis and is very common in individuals who have had the infection. It may be the only lesion present in so-called latent lues with a persistent positive Wassermann, and emphasizes the importance of examining all such patients for possible cardiovascular involvement. It is a frequent concomitant of paresis and tabes, especially the rudimentary form, occurring in about 80 per cent. of parasyphilitics.

Infection of the nervous system probably takes place during the secondary stage. A low-grade meningitis may exist for years or the spirochetes may remain quiescent for years until called into activity. In paresis a mantling infiltration of lymphocytes and plasma cells is found in the adventitial lymph spaces of the meninges and encephalon. From its pathological anatomy, which has been studied in all stages, it is much easier to comprehend this condition than the tract degeneration in tabes, as tabetics seldom die during the early period of the affection. The few pathological examinations which have been made, reveal, however, changes in the meninges about the posterior roots between the ganglion and the cord. It is not so difficult to understand how an infiltration in this region by pressure could produce degeneration of the afferent fibers extending to the posterior columns and leading to an ascending tract degeneration following the well-known law that a destruction of the neuron is followed by degeneration along its distribution. This explanation is a much more plausible one than a primary degeneration without inflammatory manifestations.

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THE VALUE OF CERTAIN TESTS FOR DIAGNOSIS AND PROGNOSIS IN CHRONIC NEPHRITIS.

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Numerous tests have been devised from time to time in order to make an early diagnosis or prognosis in chronic nephritis. Also by a study of the responses to certain tests attempts have been made in recent years to classify the different types of chronic nephritis.

Of these different tests the examination of the urine for albumin and casts and the determination of the blood-pressure have been used pretty generally, especially for making a diagnosis of renal trouble. Recently, Rowntree and Geraghty[1] devised the now well-known test which depends upon the elimination of phenolsulphone-

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[1] Jour. Pharm. and Exp. Ther., 1910, i, 579.